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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,550	12/19/2000	Julia Y. Ljubimova	18810-80364	6437

7590 06/13/2005

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/741,550	LJUBIMOVA ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,9,13-16,18,21-24,26,28,29,32-34,36,60 and 75-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,9,13-16,18,21-24,26,28,29,32-34,36,60 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Attachment A.

DETAILED ACTION

1. This action is in response to the papers filed March 22, 2005. Currently, claims 1, 3-5, 7, 9, 13-16, 18, 21-24, 26, 28-29, 32-34, 36, 60, 75-80 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims and the arguments.

4. This action contains new grounds of rejection necessitated by Amendment.

5. This action is FINAL.

Claim Rejections - 35 USC § 112-Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-5, 7, 9, 13-16, 18, 21-24, 26, 28-29, 32-34, 36, 60, 75-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods for detecting glioma in a human subject by comparing the expression level of laminin alpha4-specific mRNA or laminin

alpha 4 subunit protein to normal controls, wherein overexpression of laminin alpha4-specific mRNA or protein indicates the presence of a malignant tumor.

The claims are very broadly drawn to detecting a laminin alpha4-specific mRNA or laminin alpha4 subunit protein. The amendments to the claim to encompass the laminin alpha4 specific mRNA can be amplified using SEQ ID NO: 1 and SEQ ID NO: 2 as a primer pair. First, it is noted that the claim does not require actually amplifying the laminin alpha4 mRNA with SEQ ID NO: 1 and 2, but rather provides that they may be amplified with these sequences. Further, amplification tow primers does not describe the amplicon. Finally, the claims provide no description for the alpha4 subunit protein. Thus the claim remains broadly drawn to aspects not described by the instant specification.

The specification specifically states that laminin alpha4 specific polynucleotide sequence include mRNA sequence at least 5-30 contiguous nucleotides long, and preferably at least about 45 contiguous nucleotides long. A laminin alpha4 specific mRNA can be but is not necessarily an mRNA species containing a nucleotide sequence that encodes a functional laminin alpha4 subunit or a fragment thereof. Also, included among laminin alpha4 specific mRNAs are splice variants" (page 20, lines 10-20). This extremely large genus of nucleic acids has not been provided in the instant specification or the art at the time the invention was made. Further, the specification fails to provide evidence that splice-variants, mutations, homologs and other variations of the laminin alpha4 specific mRNAs are associated with malignant tumors. The art teaches mutations or splice variants in genes may significantly alter the expression

patterns of genes such that they are no longer commensurate in expression with the wild type gene. It is unpredictable that the skilled artisan could use the murine homolog of laminin alpha4 to detect tumors in humans. There is no evidence that homologs would have significant homology to detect and diagnose tumors. Based upon the evidence in the specification, the declaration and the post filing date art, detection of laminin-9 does not appear to be predictably associated with tumors.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined

whether a representative number of species have been described by their complete structure.

In the instant case, Applicant has defined only single Genbank Accession Number provided in the art. The specification has been amended to delete the reference to Z99289 which did not appear to incorporate the sequence into the specification nor does the specification appear to state that Z99289 is SEQ ID NO: 1. The Genbank Identifier Z99289 is a sequence that has been updated 3 times prior to the date of filing. Z99289.1 was first seen in NCBI on September 20, 1997. This sequence was altered on October 2, 1997, again on October 31, 1997 and again on May 30, 1998. Each of these changes was prior to the filing date of the instant application. These changes are evident based upon the mere number of base pairs in the listing. The changes have decreased over time from over 240,000bp to 190,778 bp. Thus, it is clear that the record for Genbank Accession Z99289 has changed over time. The instant specification has not described which sequence was used in the specification. Further, the Genbank sequence and SEQ ID NO: 1 is 190,778 bp in length and is directed to chromosome 6q21. There is no description or disclosure of the laminin alpha4 specific mRNA in the annotations of the sequence. It is highly likely and most probable that additional sequences for genes and DNA are located on 6q21 which are not laminin alpha4. The claims have been amended to require "complementary to a nucleic acid of SEQ ID NO: 1." The specification has not described the sequence for laminin alpha4 specific mRNA. Thus, the claim encompasses using probes which are outside laminin alph4 for detection which does not appear to be supported by the instant

specification. The specification states that gene expression microarrays have gene sequences of about 500-5000 base pairs in length. A sequence of 190,778 is clearly outside the size range discussed for the gene expression array.

The specification has been amended to add Genbank Accession Number NM_002290. As noted in the new matter rejection below, it is not clear where the support for this new sequence may be found in the original disclosure. NM_002290 is suggested to be a more correct GenBank Accession Number, however NM_002290 has similarly been amended and updated numerous times. The sequence has been updated on at least two occasions. Addition of this new sequence constitutes new matter.

Therefore, as discussed above, the very broad genus of alpha4-specifc mRNA sequences has not been described because neither the specification nor the art teaches a representative number of mutations, homologs, splice variants which are encompassed by the genus. Moreover, there is no identification of a laminin alph4 protein. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been amened to require that the laminin alpha4 specific mRNA can be amplified using SEQ ID NO: 2 as a primer pair. This argument has been thoroughly reviewed, but is not found persuasive. First the claim states that the laminin alph4 specific mRNA "can be" amplified using SEQ ID NO: 1 and 2 which does not indicate that SEQ ID NO: 1 and 2

are embedded within the sequence, as primers that have some mismatches may hybridize and amplify variant sequences. Many studies use primer to the human gene, for example to pull out homologous sequences, therefore the claims remain drawn to homologus sequences and variants. Moreover, while the response asserts that one splice variant of laminin alpha4 chain has been described post filing, the response further states that this variant differs from the original laminin alpha4 sequence by 21 nucleotides, such that additional 7 amino acids are present in the protein. Given this situation, the primers would still bind to the sequence, however depending on the location of the inserted 21 nucleotides would only amplify a portion of the laminin alpha splice variant or would contain a larger amplicon if the additional nucleotides were located between the binding sites for the primers. Either way, as described by the response, the primers would appear to hybridize to the sequence and allow for amplification of the variant sequence which was not described in the instant specification. Further, as discussed above, the rodent laminin alpha4 chain differs from the human laminin alpha4 analyzed, however, the primers would hybridize under less stringent conditions. Attached is an alignment of NM_002290 (a human laminin alpha4 mRNA) and NM_010681 (a mouse laminin, alpha 4 mRNA). The sequences are 86% identical. The primer of SEQ ID NO: 1 binds to position 4108-4134 of SEQ ID NO: 1 and to nucleotides 4155-4181 of the mouse sequence. There are 4 mismatches between the 26 nucleotides which would appear to allow for hybridization. Further SEQ ID NO: 2 is located at positions 4442-4469 of the laminin alpha 4 from the human and nucleotides 4490-4516 of the mouse laminin alpha 4 gene. Within this binding region

there appears to be only 2 mismatches. Therefore, while the claims have been amended to contain "can be amplified using SEQ ID NO: 1 and 2 as a primer pair" this does not appear to limit the claim to any particular sequence. The claim remains drawn to broadly encompasses isoforms, splice variants, homologs and additional sequence which have not been described by the instant specification.

Moreover, there is no identification of a laminin alph4 protein.

Thus for the reasons above and those already of record, the rejection is modified and maintained.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3-5, 7, 9, 13-16, 18, 21-24, 26, 28-29, 32-34, 36, 60, 75-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to methods for detecting <u>any</u> malignant tumor in a human subject by comparing the expression level of laminin alpha4-specific mRNA complenetary to a nucleic acid of SEQ ID NO: 1 or laminin alph4 protein to normal

controls, wherein overexpression of laminin alpha4-specific mRNA or protein indicates the presence of a malignant tumor.

The art, namely Ringelmann et al. (Experimental Cell Research, Vol. 246, pages 165-182, 1999) teaches strong interstitial expression of laminin alpha4 mRNA in myogenic tissues of embryonic but not mature mice, implicating a role for this laminin alpha chain in myogenesis (page 166, col. 2). Additionally, Previtali et al. (Glia, Vol. 26, pages 55-63, 1999) teaches the abnormal expression of a laminin receptor, alpha6beta4 integrin in human astrocytomas (abstract). Tysnes et al. (Int. J. Devl. Neuroscience, Vol. 17, No. 5-6, pages 531-539, 1999) teaches "compared to normal astrocytes, neoplastic astrocytes in situ have shown increased expression of the laminin receptor alpha3 and beta1 integrin subunits" (page 538).

Ljubimova et al. (Cancer Research, Vol. 61, No. 14, pp 5601-5610, July 2001) teaches that laminin-8 and laminin-9 have different effects on the recurrence of tumors. Thus, it is clear that mere detection of alpha4, without more does not accurately provide an analysis of recurrence rates.

The claims are very broadly drawn to detecting a laminin alpha4-specific mRNA. The specification specifically states that laminin alpha4 specific polynucleotide sequence include mRNA sequence at least 5-30 contiguous nucleotides long, and preferably at least about 45 contiguous nucleotides long. A laminin alpha4 specific mRNA can be but is not necessarily an mRNA species containing a nucleotide sequence that encodes a functional laminin alpha4 subunit or a fragment thereof. Also, included among laminin alpha4 specific mRNAs are splice variants" (page 20, lines 10-

20). This extremely large genus of nucleic acids has not been provided in the instant specification or the art at the time the invention was made. Further, the specification fails to provide evidence that splice-variants, mutations, homologs and other variations of the laminin alpha4 specific mRNAs are associated with malignant tumors. The art teaches mutations or splice variants in genes may significantly alter the expression patterns of genes such that they are no longer commensurate in expression with the wild type gene. It is unpredictable that the skilled artisan could use the murine homolog of laminin alpha4 to detect tumors in humans. There is no evidence that homologs would have significant homology to detect and diagnose tumors.

In the instant case, Applicant has defined only single Genbank Accession Number provided in the art. The specification does not appear to incorporate the sequence into the specification nor does the specification appear to state that Z99289 is SEQ ID NO: 1. The Genbank Identifier Z99289 is a sequence that has been updated 3 times prior to the date of filing. Z99289.1 was first seen in NCBI on September 20, 1997. This sequence was altered on October 2, 1997, again on October 31, 1997 and again on May 30, 1998. Each of these changes was prior to the filing date of the instant application. These changes are evident based upon the mere number of base pairs in the listing. The changes have decreased over time from over 240,000bp to 190,778 bp. Thus, it is clear that the record for Genbank Accession Z99289 has changed over time. The instant specification has not described which sequence was used in the specification. Further, the Genbank sequence and SEQ ID NO: 1 is 190,778 bp in length and is directed to chromosome 6q21. There is no description or disclosure of the

laminin alpha4 specific mRNA in the annotations of the sequence. It is highly likely and most probable that additional sequences for genes and DNA are located on 6q21 which are not laminin alpha4. The claims have been amended to require "complementary to a nucleic acid of SEQ ID NO: 1." The specification has not described the sequence for laminin alpha4 specific mRNA. Thus, the claim encompasses using probes which are outside laminin alph4 for detection which does not appear to be supported by the instant specification. The specification states that gene expression microarrays have gene sequences of about 500-5000 base pairs in length. A sequence of 190,778 is clearly outside the size range discussed for the gene expression array.

Based upon the evidence in the specification, the declaration and the post filing date art, detection of laminin-9 does not appear to be predictably associated with tumors. Laminin-9 comprises the alpha-4 subunit.

With respect to Claims 28-29, 32-36, 44-45, 48-52 the post filing date are suggests that laminin-8 which was expressed mainly in blood vessel walls of GBMs and histologically normal tissues adjacent to GBMs had a shorter mean time to recurrence. Whereas laminin-9 which was expressed mainly in blood vessel walls of low-grad tumors and normal brain, had a greater time to tumor recurrence. Moreover, the specification, on pages 44-54 discuss Patient 16 and 39 and the relative recurrence rates. It is noted that claims 44 and 53 are sufficiently identical.

With respect to Claims 60-66 directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. The specification has provided no guidance as to what the

"relatively high invasiveness of the tumor" encompasses. The specification seems to illustrate a few examples where laminin alpha4 is overexpressed in astrocytoma grade II. The specification teaches that astrocytoma grade II is a lower grade malignant tumor (page 11, lines 15-16). Therefore, it is unclear how the overexpression of laminin is indicative of relatively high invasiveness of the tumor. The claims does not appear to make any distinction between low grade and higher grade tumors. Therefore, it is unclear how the tumors are classified. While the skilled artisan could provide further undue experimentation to determine a value for expression in the various types of tumors and obtain thresholds for classifying the tumors, the instant specification does not provide any predictive correlation between thresholds and classifications of tumors into grades, as required by the claims.

Moreover, the specification provides no guidance to the skilled artisan how to use the invention with respect to any type of malignant tumor. The specification does not teach expression levels in all malignant tumors, including breast, prostate, lung, colon, skin, etc. While one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, do not provide support for the use of laminin alpha4 expression as an indicator of malignant tumor. Thus it is unpredictable as to whether one could successfully use the

claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between laminin alpha4 expression and malignant tumors, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Response to Arguments and Declaration

The response traverses the rejection.

Claims 28-29, 32-34, 36, 77, remain drawn to any tumor. As discussed previously, the Declaration filed March 17, 2003, states that "like brain malignancies, malignant tumors of the breast over expresses alpha4 laminin." (page 2 of Declaration filed March 24, 2003). The specification makes clear that the laminin alpha4 subunit is particular to laminin-8, laminin-9 and laminin-14 (page 5, lines 17-19). The data in the Declaration illustrates that Laminin-8 is not expressed in normal tissue, but appears expressed in invasive carcinoma, metastases of invasive carcinoma and non-invasive carcinomas. However, Laminin-9 does not appear to be correlative of the same expression pattern. Laminin-9 is expressed in normal breast tissue (40%). This appears to indicate that the alpha4 subunit may not be responsible for the expression in breast tissues. The response argues on page 23 of the Response that "Laminin 8 requires an overexpression of both alpha4 and beta1 subunits." Therefore, the expression of Laminin 8 in breast, but not in normal may be due to the beta1 subunits since Laminin 9 does not have the same correlation.

The response asserts that the declarations clearly show that the invention is readily applicable to breast cancer as well as brain cancer (page 21 of response). This argument has been thoroughly reviewed, but is not found persuasive because the first Declaration illustrates the expression of brain metastasis of breast cancer. As stated in the prior office action, "with regard to the data presented on Page 4 of the Declaration, the western blot appears to show a lack of laminin alpha4 chain expression in normal breast tissue and its strong expression in breast cancer metastases. The Figure illustrates that the metastasis are "brain metastasis of breast cancer." Therefore, the results of the Figure appear to support a brain metastasis of breast cancer, but does not support breast cancer malignancies.

Discussion of 132 Declaration filed July 28, 2004: The declaration states that the results for malignant breast tumors are very similar to those for malignant brain tumors, but the picture is more complex because of tissue types. The declaration states that there is some alpha4 laminin expression in normal ductal tissue but not in normal breast vasculature. This statement does not appear to support that the skilled artisan would be able to take any tissue type, as instantly claimed to determine and compare expression levels to indicate tumors. The response states that 45 human breast tissue samples were used, however only 8 samples are illustrated in the declaration.

The declaration (para 10) discusses the importance of the beta1 or beta2 expression. It is noted that this is not a limitation of Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-52, 60-68. The MPEP requires that "a showing also must be commensurate

with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." Here the declaration appears to be illustrating that beta1 and alph4 (i.e. laminin-8) is essential to determining tumor status and can not be based upon alph4 alone. Specifically, the declaration discusses that "occasional strong expression of alpha4 in normal tissue correspond to laminin-9 but not Ln-8." Thus, the alpha4 nucleic appears to be only be informative when expressed with beta1. The declaration superficially states that "to take the expression of laph4 and beta2 into consideration, the expression pattern of the combination with alpha4 and beta1 is more predominant in cancerous tissues than normal tissues.

Analysis of Figure 1 illustrates that 50% of the normal tissues illustrated demonstrated a high expression of laminin alpha4. It is clear that in the primary invasive ductal cancers, laminin alpha 4 is not overexpressed as compared to "normal 2." Thus, to compare the expression of alpha4 subunit to normals would not provide reliable and predictable results.

Table 1 of the declaration is directed to the colocalization of alpha4 and beta1. This data further appears to support that the alpha4 chain does not provide significant and sufficient information to determine tumor status.

The response asserts that there is no possibility of mistaking breast cancer for brain cancer because all of these samples are analyzed histologically and the tissue differences between breast cancer and brain cancer are unmistakable. This argument has been thoroughly reviewed, but is not found persuasive because the claims are not drawn to determining the type of cancer. The claims are drawn to determining whether

the tissue has a tumor based upon the overexpression of alpha 4. The claims do not rely upon histological examination.

The response asserts that preliminary data for prostate cancer suggests that only relatively non-invasive prostate cancers have been evaluated. Based upon the interview, the applicant suggested that in the three prostate tumors were sampled and no alpha4 expression was found. Thus, the assertions by the applicant that all cancers overexpress laminin alpha4, does not appear to be consistent with the data provided in the specification, the art and the interviews. It is unpredictable whether additional experiment would enable the skilled artisan how to practice the claimed invention over the full scope of the claims. As stated previously, while one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue." It is well established that different cancers have expression of different genes. Thus, there is no indication that breast cancer, or any other cancer, has increased expression of alpha4 chain compared to normals, as laminin lapha4 is highly expressed in normal2. The response appears to support this conclusion by asserting that "very high levels of alpha4 and the presence of laminin 8 are markers for an aggressive tumor that has a very high potential for metastasis." Thus, the evidence provided in the declaration may support that metastasized tumors from the brain also show an increased level of alpha4, however they do not illustrate that alpha4 is overexpressed in breast cancer.

The limitations of Claim 16 appear to more closely reflect the enabled aspects of the invention. Claim 16 would require both the alpha4 and the beta 1 such that the information would yield information with regard to Laminin 8. Laminin 9 which also comprises alpha4 does not contain B1, but rather B2. Therefore by requiring alpha4 and beta1, the claims would exclude detection of laminin 9 which does not appear to have the same correlation to glioma as laminin 8.

With respect to Claims 60-66, the response argues that directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. The response (page 24 of response filed November 17, 2003) asserts that traditional ranking or grading of tumors is based strictly on histological features but histological features were unable to correctly identify aggressiveness and tendency to recur. The Examiner pointed out several points of confusion and the response asserted that this was exactly the point. However, there is no evidence that the expression patterns provide a more accurate measurement than the art established histological methods which have existed for many years and are well established. The method merely describes a generic method for assessing grades such that the higher the expression the higher the grade. The response appears to be arguing that the instant application has determined a system that "is intended to replace the traditional histological grading or ranking." This aspect of the instant invention does not appear to have been fully developed. It is noted that overexpression in particular tissues may be indicative of tumors, however there is no apparent thresholds for assigning any particular rank. In the event that overexpression

of 2x as compared to normal is ascertained, there is no guidance as to what rank or grade tumor is found. The specification does not appear to establish any ranking system, any system for tumor aggressiveness. There are not specifics in the description what various grades of tumors encompass. Therefore, the skilled artisan would not be able to establish the specific grade of a tumor with out further experimentation.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Objections

8. Claims 13-15, 79 are objected to because of the following informalities.

A) Claims 13-15, 79 depend on Claim 2 which has been cancelled.

Appropriate correction is required.

New Matter

9. The amendment filed March 22, 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: A suitable functional laminin alpha4 subunit is coded by GeneBank Accession NM_002290.

The specification has been amended to add Genbank Accession Number NM_002290. The response filed March 22, 2005 asserts that there was an inadvertent error in the specification. NM_002290 is suggested to be a more correct GenBank Accession Number. The MPEP states, "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268(CCPA 1971)." Here, the response does not provide this is an obvious error nor the appropriate correction would be recognized. The response provides that the replacement GenBank Number can be easily located by a person of skill in the art, however this is not the standard set forth by the MPEP for correction of obvious errors. Here, it does not appear that this amendment to the specification would constitute an obvious error.

Additionally, NM_002290 has been amended and updated numerous times. The sequence has been updated on at least two occasions. There is no indication which sequence was contemplated at the time of the invention. Addition of this new sequence constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 3-5, 7, 9, 13-16, 18, 21-24, 26, 28-29, 32-34, 36, 60, 75-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) 1, 3-5, 7, 9, 13-16, 18, 21-24, 26, 28-29, 32-34, 36, 60, 75-80 re indefinite because it is unclear whether the claim is drawn to a method of detecting a malignant glioma or a malignant tumor. The preamble of Claim 1 has been amended to be directed to a malignant glioma however the last clause of the method remains drawn to a malignant tumor. This rejection may be easily clarified by amending the last line of the claim to require "a malignant glioma."

Conclusion

11. No claims allowable.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
June 8, 2005

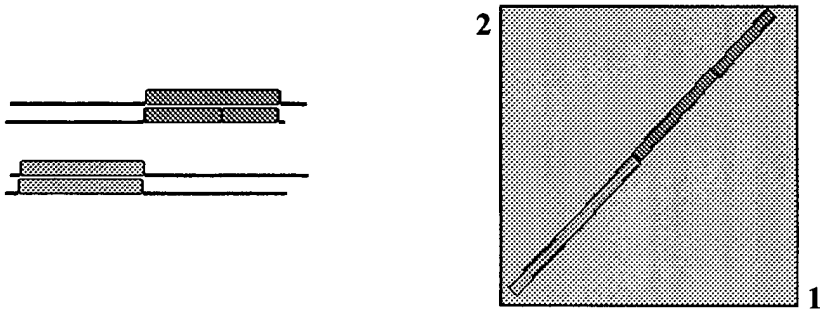
Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.10 [Oct-19-2004]

Match: 1 Mismatch: -2 gap open: 5 gap extension: 2
x_dropoff: 30 expect: 10.000 wordsize: 11 Filter ☑ Align

Sequence 1 gi 9845494 Homo sapiens laminin, alpha 4 (LAMA4), mRNA **Length** 6297 (1 .. 6297)
Sequence 2 gi 46275825 Mus musculus laminin, alpha 4 (Lama4), mRNA **Length** 5915 (1 .. 5915)



NOTE: The statistics (bitscore and expect value) is calculated based on the size of nr database

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence

```
Score = 3228 bits (1679), Expect = 0.0
Identities = 2452/2843 (86%), Gaps = 6/2843 (0%)
 Strand = Plus / Plus
```

```
Query:              2894 gcagatcagtttatcctgtacctcggaagcaaaaacgccaaaaaagagtatatgggtctt 2
                         ||||||||||||| |||| ||||||||||||||||||||||||||||| || ||||||||
Sbjct:              2941 gcagatcagtttgtcctctacctcggaagcaaaaacgccaaaaaagaatacatgggtctg 3
laminin, alpha 4 873   A  D  Q  F  V  L  Y  L  G  S  K  N  A  K  K  E  Y  M  G  L

Query:              2954 gcaatcaaaaatgataatctggtatacgtctataatttgggaactaaagatgtggagatt 3
                         |||||||||||||||| |||||||||| || |||||||| | |||||||||| |||
Sbjct:              3001 gcaatcaaaaatgataacctggtatacgtttacaatttggggatgaaagatgtggaaatt 3
laminin, alpha 4 893   A  I  K  N  D  N  L  V  Y  V  Y  N  L  G  M  K  D  V  E  I

Query:              3014 cccctggactccaagcccgtcagttcctggcctgcttacttcagcattgtcaagattgaa 3
                         | |||||| |||||||| || || |||||||| |||||||| || ||||||||||||||
Sbjct:              3061 ctcctggattccaagcctgtgagctcctggcccgcttactttagtattgtcaagattgaa 3
laminin, alpha 4 913   L  L  D  S  K  P  V  S  S  W  P  A  Y  F  S  I  V  K  I  E

Query:              3074 agggtgggaaaacatggaaaggtgtttttaacagtcccgagtctaagtagcacagcagag 3
                         ||||| || |||||| |||||||||| || |||||||| |||||| ||||||||||||||
```

```
Sbjct:           3121 agggtagggaaacacggaaaggtgttcttgacagtccccagtctcagtagcacagcagaa 3
laminin, alpha 4 933   R  V  G  K  H  G  K  V  F  L  T  V  P  S  L  S  S  T  A  E

Query:           3134 gaaaagttcattaaaaaggggggaattttcgggagatgactctctgctggacctggaccct 3
                      ||||||||  |||||  ||||||||  |||  |  ||||||||||  |||||||  |||  ||||
Sbjct:           3181 gaaaagtttattaagaaggggggagtttgcaggagatgactccttgctggatctgacccct 3
laminin, alpha 4 953   E  K  F  I  K  K  G  E  F  A  G  D  D  S  L  L  D  L  T  P

Query:           3194 gaggacacagtgttttatgttggtggagtgccttccaacttcaagctccctaccagctta 3
                      ||||||||  ||||||||  ||||||||  ||||||  |  ||||||||||||||  ||||||||
Sbjct:           3241 gaggacactgtgttttacgttggtggggtgcctgcgaacttcaagctccctgccagctta 3
laminin, alpha 4 973   E  D  T  V  F  Y  V  G  G  V  P  A  N  F  K  L  P  A  S  L

Query:           3254 aacctgcctggctttgttggctgcctggaactggccactttgaataatgatgtgatcagc 3
                      ||||||||  |||    ||||||||  ||  |||||||||  ||||||||||||||||||||
Sbjct:           3301 aacctgcccagctactcaggctgcctagagctggccactctgaataatgatgtgatcagc 3
laminin, alpha 4 993   N  L  P  S  Y  S  G  C  L  E  L  A  T  L  N  N  D  V  I  S

Query:           3314 ttgtacaactttaagcacatctataatatggacccctccacatcagtgccatgtgcccga 3
                      ||||||||||||  ||||||||||||||||||||||  ||  ||  |  ||||||||  ||||||  |
Sbjct:           3361 ttgtacaacttcaagcacatctataatatggatccatcaaagtcagtgccctgtgccagg 3
laminin, alpha 4 1013  L  Y  N  F  K  H  I  Y  N  M  D  P  S  K  S  V  P  C  A  R

Query:           3374 gataagctggccttcactcagagtcgggctgccagttacttcttcgatggctccggttat 3
                      |||||  |||||  ||||||||||||  ||||||||||  ||||||||||||||||||  |||||
Sbjct:           3421 gataaactggctttcactcagagtagggctgccagctacttcttcgatggctccagttat 3
laminin, alpha 4 1033  D  K  L  A  F  T  Q  S  R  A  A  S  Y  F  F  D  G  S  S  Y

Query:           3434 gccgtggtgagagacatcacaaggagagggaaatttggtcaggtgactcgctttgacata 3
                      ||  ||||||||  ||||||||  ||||||||||  ||||||||||||||||||||||||||
Sbjct:           3481 gcagtggtgagggacatcacgaggagagggaagtttggtcaggtgactcgctttgacata 3
laminin, alpha 4 1053  A  V  V  R  D  I  T  R  R  G  K  F  G  Q  V  T  R  F  D  I

Query:           3494 gaagttcgaacaccagctgacaacggccttattctcctgatggtcaatggaagtatgttt 3
                      |||  |  ||||||||||||||||  ||||||  |  ||||||||||||||||  |||||||||
Sbjct:           3541 gaaatccgaacaccagctgacaatggccttgtgctcctgatggtcaatggcagtatgttt 3
laminin, alpha 4 1073  E  I  R  T  P  A  D  N  G  L  V  L  L  M  V  N  G  S  M  F

Query:           3554 ttcagactggaaatgcgcaatggttacctacatgtgttctatgattttggattcagcagt 3
                      |||||  ||  ||||||||||||||  ||||||||||||||||||||  ||||||||||||  |
Sbjct:           3601 ttcagcctcgaaatgcgcaatggctacctacatgtgttctatgactttggattcagcaat 3
laminin, alpha 4 1093  F  S  L  E  M  R  N  G  Y  L  H  V  F  Y  D  F  G  F  S  N

Query:           3614 ggccgtgtgcatcttgaagatacgttaaagaaagctcaaattaatgatgcaaaataccat 3
                      ||||  ||||||||||||||  |||||  ||  |||||  ||  ||||||||||  |||||  |||
Sbjct:           3661 ggccccgtgcatcttgaagacacgttgaaaaaagcccagattaatgatgcgaaatatcat 3
laminin, alpha 4 1113  G  P  V  H  L  E  D  T  L  K  K  A  Q  I  N  D  A  K  Y  H

Query:           3674 gagatctcaatcatttaccacaatgataagaaaatgatcttggtagttgacagaaggcat 3
                      ||||||||||||||||  |||||  ||  ||  ||||||||  |||||  ||  ||||||  ||||
```

```
Sbjct:           3721 gagatctcaatcatttatcacaacgacaaaaaaatgattttggtggtggacagacggcac 3
laminin, alpha 4 1133  E  I  S  I  I  Y  H  N  D  K  K  M  I  L  V  V  D  R  R  H

Query:           3734 gtcaagagcatggataatgaaaagatgaaaatacctttacagatatatacattggagga 3
                      || |||||||  || |||||  ||||  || ||  |||||  ||  ||  ||  |||||  |||||
Sbjct:           3781 gttaagagcacagacaatgagaagaaaaagattcctttcacggacatctacatcggaggt 3
laminin, alpha 4 1153  V  K  S  T  D  N  E  K  K  K  I  P  F  T  D  I  Y  I  G  G

Query:           3794 gctcctccagaaatcttacaatccagggccctcagagcacaccttcccctagatatcaac 3
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Sbjct:           3841 gcgccccaagaagtcttacagtccaggaccctaagagcacaccttcccctagatatcaac 3
laminin, alpha 4 1173  A  P  Q  E  V  L  Q  S  R  T  L  R  A  H  L  P  L  D  I  N

Query:           3854 ttcagaggatgcatgaagggcttccagttccaaaagaaggacttcaatttactggagcag 3
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Sbjct:           3901 tttaggggggtgcatgaaggggttccagttccaaaagaaagatttcaatttactggagcag 3
laminin, alpha 4 1193  F  R  G  C  M  K  G  F  Q  F  Q  K  K  D  F  N  L  L  E  Q

Query:           3914 acagaaaccctgggagttggttatggatgcccagaagactcacttatatctcgcagagca 3
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Sbjct:           3961 acagaaaccctaggagttggttatggatgcccagaggactctctgatatctcgcagagca 4
laminin, alpha 4 1213  T  E  T  L  G  V  G  Y  G  C  P  E  D  S  L  I  S  R  R  A

Query:           3974 tatttcaatggacagagcttcattgcttcaattcagaaaatatctttctttgatggcttt 4
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Sbjct:           4021 tatttcaatgggcaaagttttattgcttcaattcagaaaatatctttctttgatggcttt 4
laminin, alpha 4 1233  Y  F  N  G  Q  S  F  I  A  S  I  Q  K  I  S  F  F  D  G  F

Query:           4034 gaaggaggttttaatttccgaacattacaaccaaatgggttactattctattatgcttca 4
                      ||||||||  ||  ||||||||||||||||  ||||||||||||||||||||  ||  |  |||
Sbjct:           4081 gaaggaggcttcaatttccgaacattacagccaaatgggttactattctactacacatca 4
laminin, alpha 4 1253  E  G  G  F  N  F  R  T  L  Q  P  N  G  L  L  F  Y  Y  T  S

                                                    Fig. 1
Query:           4094 gggtcagacgtgttctccatctcactggataatggtactgttcatcatggatgtaaaggga 4
                      |||||  ||||||||  |||||  ||||||||  ||  ||  |||||  |||||||  ||||||||
Sbjct:           4141 gggtcggacgtgttttccatttcactggacaacggcactgttgtcatggacgtaaagggc 4
laminin, alpha 4 1273  G  S  D  V  F  S  I  S  L  D  N  G  T  V  V  M  D  V  K  G

Query:           4154 atcaaagttcagtcagtagataagcagtacaatgatgggctgtcccacttcgtcattagc 4
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Sbjct:           4201 atcaaggtcatgtcaacagacaagcagtaccacgatgggctgccccacttcgtggtcacc 4
laminin, alpha 4 1293  I  K  V  M  S  T  D  K  Q  Y  H  D  G  L  P  H  F  V  V  T

Query:           4214 tctgtctcacccacaagatatgaactgatagtagataaaagcagagttgggagtaagaat 4
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Sbjct:           4261 tccatctcagacacaagatatgaactggtagtagacaaaagccgacttcgagggaagaat 4
laminin, alpha 4 1313  S  I  S  D  T  R  Y  E  L  V  V  D  K  S  R  L  R  G  K  N

Query:           4274 cctaccaaagggaaaatagaacagacacaagcaagtgaaaagaagttttacttcggtggc 4
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```

```
Sbjct:           4321 ccaacaaaagggaaggcagagcagactcaaacaactgagaagaagttctactttggtggc 4
laminin, alpha 4 1333  P  T  K  G  K  A  E  Q  T  Q  T  T  E  K  K  F  Y  F  G  G

Query:           4334 tcaccaatcagtgctcagtatgctaatttcactggctgcataagtaatgcctactttacc 4
                      ||||| |||||| |||||||||||||||||||||| || ||||| ||||||||||||||
Sbjct:           4381 tcacccatcagtcctcagtatgctaatttcactggatgtataagcaatgcctactttacc 4
laminin, alpha 4 1353  S  P  I  S  P  Q  Y  A  N  F  T  G  C  I  S  N  A  Y  F  T

Query:           4394 agggtggatagagatgtggaggttgaagatttccaacggtatactgaaaaggtccacact 4
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Sbjct:           4441 aggttggatagagatgtggaagtcgaagacttccagcgctattctgaaaaggtccacact 4
laminin, alpha 4 1373  R  L  D  R  D  V  E  V  E  D  F  Q  R  Y  S  E  K  V  H  T

Query:           4454 tctctttatgagtgtccattgagtcttcaccattgtttctcctccatnnnnnnnnnnnn 4
                      ||.|| ||||||||||| |||||||| ||||| |||||||||| ||
Sbjct:           4501 tcactctatgagtgtccgattgagtcgtcacctctgtttctccttcacaaaaaaggaaaa 4
laminin, alpha 4 1393  S  L  Y  E  C  P  I  E  S  S  P  L  F  L  L  H  K  K  G  K

Query:           4514 nntttatccaagcctaaagcaagtcagaataaaaagggagggaaaagtaaagatgcacct 4
                        || || ||||||||| ||      || ||| |||||| ||| ||||| ||||| |||
Sbjct:           4561 gaattctcaaagcctaaaaca------aacaaacagggagagaagagtaaggatgcgcct 4
laminin, alpha 4 1413  E  F  S  K  P  K  T       N  K  Q  G  E  K  S  K  D  A  P

Query:           4574 tcatgggatcctgttgctctgaaactcccagagcggaatactccaagaaactctcattgc 4
                      |||||||||||| ||| ||||| | |  || | ||| |||||||| | || || |||
Sbjct:           4615 tcatgggatcctattggcctgaagtttctggaacagaaagctccaagagattcccactgc 4
laminin, alpha 4 1431  S  W  D  P  I  G  L  K  F  L  E  Q  K  A  P  R  D  S  H  C

Query:           4634 caccttccaacagccctagagcaatagagcacgcctatcaatatggaggaacagccaac 4
                      ||||| |||| |||||| || |||||||| || |||||||||||||| || || ||||||
Sbjct:           4675 cacctctccagcagccccagggcaatagaacatgcctatcaatatggcggcacggccaac 4
laminin, alpha 4 1451  H  L  S  S  S  P  R  A  I  E  H  A  Y  Q  Y  G  G  T  A  N

Query:           4694 agccgccaagagtttgaacacttaaaaggagattttggtgccaaatctcagttttccatt 4
                      || ||||| |||||||||||| | ||||||||||||||| ||||| |||||| |||||
Sbjct:           4735 agtcgccaggagtttgaacacgaacaaggagattttggtgaaaaatcccagtttgccatt 4
laminin, alpha 4 1471  S  R  Q  E  F  E  H  E  Q  G  D  F  G  E  K  S  Q  F  A  I

Query:           4754 cgtctgagaactcgttcctcccatggcatgatcttctatgtctcagatcaagaagagaat 4
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Sbjct:           4795 cgtctgaagacccgttcctcacatgggatgattttctatgtctcagaccaagaagagaat 4
laminin, alpha 4 1491  R  L  K  T  R  S  S  H  G  M  I  F  Y  V  S  D  Q  E  E  N

Query:           4814 gacttcatgactctatttttggcccatggccgcttggtttacatgtttaatgttggtcac 4
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Sbjct:           4855 gatttcatgaccctgttcttggcccatggtcgcttggtctttatgtttaatgttggccat 4
laminin, alpha 4 1511  D  F  M  T  L  F  L  A  H  G  R  L  V  F  M  F  N  V  G  H

Query:           4874 aaaaaactgaagattagaagccaggagaaatacaatgatggcctgtggcatgatgtgata 4
                      || ||||||||||||||||||||||||||||||||||||||||| ||||||||||||||||
```
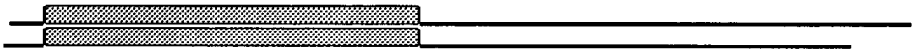

```
Sbjct:              4915 aagaaactgaagattagaagccaggagaaatacaatgatggattgtggcatgatgtgata 4
laminin, alpha 4 1531  K  K  L  K  I  R  S  Q  E  K  Y  N  D  G  L  W  H  D  V  I

Query:              4934 tttattcgagaaaggagcagtggccgactggtaattgatggtctccgagtcctagaagaa 4
                         ||||||||  ||||  |||||||||  ||||||||  ||||||||||  ||||||||||||||
Sbjct:              4975 tttattcgggaaaagagcagtggtcgactggtcattgatggtctacgagtcctagaagaa 5
laminin, alpha 4 1551  F  I  R  E  K  S  S  G  R  L  V  I  D  G  L  R  V  L  E  E

Query:              4994 agtcttcctcctactgaagctacctggaaaatcaagggtcccatttatttgggaggtgtg 5
                         ||  |||||  ||||  ||  |||  |||||||||||||||||||||||||  |||||||  |||
Sbjct:              5035 aggcttccccctagtggcgctgcctggaaaatcaagggtcccatttatctgggaggagtg 5
laminin, alpha 4 1571  R  L  P  P  S  G  A  A  W  K  I  K  G  P  I  Y  L  G  G  V

Query:              5054 gctcctggaaaggctgtgaaaaatgttcagattaactccatctacagttttagtggctgt 5
                         |||||  ||||  ||  ||||||||||  |||||||  ||||  |||||||  ||  ||||||||
Sbjct:              5095 gctcccggaagagccgtgaaaaatgtccagattacctccgtctacagcttcagtggctgc 5
laminin, alpha 4 1591  A  P  G  R  A  V  K  N  V  Q  I  T  S  V  Y  S  F  S  G  C

Query:              5114 ctcagcaatctccagctcaatggggcctccatcacctctgcttctcagacattcagtgtg 5
                         ||  ||||||||||||||||||  ||||||||||||||  ||||||||  ||  ||  ||  |||
Sbjct:              5155 cttggcaatctccagctcaatggtgcctccatcacctccgcttctcaaacgtttagcgtg 5
laminin, alpha 4 1611  L  G  N  L  Q  L  N  G  A  S  I  T  S  A  S  Q  T  F  S  V

Query:              5174 acccccttgctttgaaggccccatggaaacaggaacttacttttcaacagaaggaggatac 5
                         ||||||||||||||||||  ||  ||||||||||||||||||  |||||  ||||||||  ||  ||
Sbjct:              5215 acccccttgctttgaagggccaatggaaacaggaacttatttttccacagaaggcggctat 5
laminin, alpha 4 1631  T  P  C  F  E  G  P  M  E  T  G  T  Y  F  S  T  E  G  G  Y

Query:              5234 gtggttctagatgaatctttcaatattggattgaagtttgaaattgcatttgaagtccgt 5
                         ||||||||||||||  ||||||||||||||  ||  ||  ||||||||||||  ||||||||||
Sbjct:              5275 gtggttctagatgagtctttcaatattgggttaaaatttgaaattgcctttgaagtccgc 5
laminin, alpha 4 1651  V  V  L  D  E  S  F  N  I  G  L  K  F  E  I  A  F  E  V  R

Query:              5294 cccagaagcagttccggaaccctggtccacggccacagtgtcaatggggagtacctaaat 5
                         |||  |  ||||||||  ||||||||  |||||  ||||||||  |||||  |||||  ||
Sbjct:              5335 ccccggagcagttctggaacccttgtccatggccacagcgtcaacggggaatacctgaac 5
laminin, alpha 4 1671  P  R  S  S  S  G  T  L  V  H  G  H  S  V  N  G  E  Y  L  N

Query:              5354 gttcacatgaaaaatggacaggtcatagtgaaagtcaataatggcatcagagatttttcc 5
                         ||  |||||||  |||  ||||||||||||||||  |||||  ||  ||  |||||||  |||||
Sbjct:              5395 gtgcacatgagaaacggacaggtcatagtgaaggtcaacaacggtgtcagagacttttct 5
laminin, alpha 4 1691  V  H  M  R  N  G  Q  V  I  V  K  V  N  N  G  V  R  D  F  S

Query:              5414 acctcagtaacacccaagcagagtctctgtgatggcagatggcacagaattacagttatt 5
                         ||||||||||  |||||||||  ||||||||||||||||||||||||||||||||||||||||
Sbjct:              5455 acctcagtaactcccaagcagaatctctgtgatggcagatggcacagaattacagttatt 5
laminin, alpha 4 1711  T  S  V  T  P  K  Q  N  L  C  D  G  R  W  H  R  I  T  V  I

Query:              5474 agagattctaatgtggttcagttggatgtggactctgaagtgaaccatgtggttggaccc 5
                         ||||||||  ||  ||||||||||||||||  |||||  ||||||||||||||  |||||  ||
```

```
Sbjct:           5515 agagattcaaacgtggttcagttggatgtagactcagaagtgaaccatgtagttgggccg 5
laminin, alpha 4 1731  R  D  S  N  V  V  Q  L  D  V  D  S  E  V  N  H  V  V  G  P

Query:           5534 ctgaatccaaaaccaattgatcacagggagcctgtgtttgttggaggtgttccagaatct 5
                      |||||||||| ||| ||||||||||||||||||||||||||||||||||||||| |||
Sbjct:           5575 ttgaatccaaagccagttgatcacagggagcctgtgtttgttggaggtgttccagagtct 5
laminin, alpha 4 1751  L  N  P  K  P  V  D  H  R  E  P  V  F  V  G  G  V  P  E  S

Query:           5594 ctactgacaccacgcttggcccccagcaaacccttcacaggctgcatacgccactttgtg 5
                      |||||||||||||| ||||| |||||||||||||||| |||||||| ||||||||||
Sbjct:           5635 ttactgacaccacgtttggctcccagcaaacccttcaccggctgcatccgccactttgta 5
laminin, alpha 4 1771  L  L  T  P  R  L  A  P  S  K  P  F  T  G  C  I  R  H  F  V

Query:           5654 attgatggacacccagtgagcttcagtaaagcagccctggtcagcggcgccgtaagcatc 5
                      |||||  | | ||| |||||||||||||||| |||||||||| || || || ||||||
Sbjct:           5695 attgacagccgccctgtgagcttcagtaaagctgccctggtcagtggtgctgtgagcatc 5
laminin, alpha 4 1791  I  D  S  R  P  V  S  F  S  K  A  A  L  V  S  G  A  V  S  I

Query:           5714 aactcctgtccagcagcctgaca 5736
                      |||||||||||  ||||||||||
Sbjct:           5755 aactcctgtcccacagcctgaca 5777
laminin, alpha 4 1811  N  S  C  P  T  A ^^^
```

Score = 2775 bits (1443), Expect = 0.0
Identities = 2223/2613 (85%)
Strand = Plus / Plus



```
Query:           254  ggaagagcactactggatgtcagcggagaaatggctttgagctcagcctggcgctcggtt 3
                      ||||| || ||  || || || || |||| |||| || |||| |||| ||| |||| ||
Sbjct:           295  ggaagggccctgttgaatatctgcagagagatgggttggagcacagcttggtgctcagtc 3
laminin, alpha 4 1                                  M  G  W  S  T  A  W  C  S  V

Query:           314  ctgcctctgtggctcctctggagcgctgcctgctcccgcgccgcgtccggggacgacaac 3
                      ||| | ||||||||||||||| | |||| ||||||| ||| ||||| ||||||| |||
Sbjct:           355  ctggccctgtggctcctctggtgtgctgtctgctccaacgcagcgtcaggggacggcaat 4
laminin, alpha 4 11    L  A  L  W  L  L  W  C  A  V  C  S  N  A  A  S  G  D  G  N

Query:           374  gcttttccttttgacattgaagggagctcagcggttggcaggcaagacccgcctgagacg 4
                      || |||||||||||||| || |||||| ||| ||| |||||||||||||  | |||||
Sbjct:           415  gcgtttccttttgacatcgaggggagcgcagtggtcggcaggcaagacccatcggagact 4
laminin, alpha 4 31    A  F  P  F  D  I  E  G  S  A  V  V  G  R  Q  D  P  S  E  T

Query:           434  agcgaaccccgcgtggctctgggacgctgccgcctgcggccgagaaatgcaatgctgga 4
                      |||||  |  ||||| | |||||||||||||||||| || |||| |||  | ||||||
Sbjct:           475  agcgactcaggcgtgacactgggacgcctgccgcctgctgctgagagatgtgacgctgga 5
laminin, alpha 4 51    S  D  S  G  V  T  L  G  R  L  P  P  A  A  E  R  C  D  A  G

Query:           494  ttctttcacaccctgtcgggagaatgtgtgccctgcgactgtaatggcaattccaacgag 5
                      ||||| | ||| ||||| |||||||||||  ||||| |||||||||||||||||| | |||
```

```
Sbjct:          535  ttcttccgcacactgtcaggagaatgtgcaccctgtgactgtaatggcaattcccatgag 5
laminin, alpha 4 71    F  F  R  T  L  S  G  E  C  A  P  C  D  C  N  G  N  S  H  E

Query:          554  tgtttggacggctcaggatactgtgtgcactgccagcggaacacaacaggagagcactgt 6
                     ||  |||||  |||||  ||||  ||||  ||||||||||||||||||||||||||||||||||
Sbjct:          595  tgcttggatggctccggattctgtctgcactgccagcggaacacaacaggagagcactgt 6
laminin, alpha 4 91    C  L  D  G  S  G  F  C  L  H  C  Q  R  N  T  T  G  E  H  C

Query:          614  gaaaagtgtctggatggttatatcggagattccatcaggggagcaccccaattctgccag 6
                     |||||  ||||||||||||  |||||  |||||  ||||||||  ||  ||||||  |||||||||
Sbjct:          655  gaaaaatgtctggatggctatattggagactccatcagaggcacaccccggttctgccag 7
laminin, alpha 4 111   E  K  C  L  D  G  Y  I  G  D  S  I  R  G  T  P  R  F  C  Q

Query:          674  ccgtgcccctgtcccctgccccacttggccaattttgcagaatcctgctataggaaaaat 7
                     ||||||||||||||||  ||||||||  |||||||  ||||||||||||||||||  |||||||||
Sbjct:          715  ccgtgcccctgtcccttgccccacctggccaactttgcagaatcctgctacaggaaaaat 7
laminin, alpha 4 131   P  C  P  C  P  L  P  H  L  A  N  F  A  E  S  C  Y  R  K  N

Query:          734  ggagctgttcggtgcatttgtaacgaaaattatgctggacctaactgtgaaagatgtgct 7
                     ||||||||||||||  ||||||||  |||||  ||||  ||||||||||||||||||||||||
Sbjct:          775  ggagctgttcggtgtatttgtaaagaaaactatgttggacctaactgtgaaagatgtgcc 8
laminin, alpha 4 151   G  A  V  R  C  I  C  K  E  N  Y  V  G  P  N  C  E  R  C  A

Query:          794  cccggttactatggaaaccccttactcattggaagcacctgtaagaaatgtgactgcagt 8
                     ||  ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct:          835  cctggttactatggaaaccccttactcattggaagcacctgtaagaaatgtgactgcagt 8
laminin, alpha 4 171   P  G  Y  Y  G  N  P  L  L  I  G  S  T  C  K  K  C  D  C  S

Query:          854  ggaaattcagatcccaacctgatctttgaagattgtgatgaagtcactggccagtgtagg 9
                     ||||||||  ||||||||||||||||||||||  |||||||||  ||||||||||||  |||
Sbjct:          895  ggaaattcggatcccaacctgatctttgaagactgtgatgaaatcactggccagtgcagg 9
laminin, alpha 4 191   G  N  S  D  P  N  L  I  F  E  D  C  D  E  I  T  G  Q  C  R

Query:          914  aattgcttacgcaacaccaccggattcaagtgtgaacgttgcgctcctggctactatggg 9
                     ||  ||||||||  ||  ||||||||||||||||||||||  ||  ||  |||||  ||||||||
Sbjct:          955  aactgcttacgaaataccaccggattcaagtgtgaacgctgtgcacctggttactatgga 1
laminin, alpha 4 211   N  C  L  R  N  T  T  G  F  K  C  E  R  C  A  P  G  Y  Y  G

Query:          974  gacgccaggatagccaagaactgtgcagtgtgcaactgcgggggaggcccatgtgacagt 1
                     ||||||||||  ||||||||||||||||||||||||||  |||||  |||||  |||||||||
Sbjct:          1015 gacgccaggacagccaagaactgtgcagtgtgcaactgtgggggcggcccgtgtgacagt 1
laminin, alpha 4 231   D  A  R  T  A  K  N  C  A  V  C  N  C  G  G  G  P  C  D  S

Query:          1034 gtaaccggagaatgcttggaagaaggttttgaaccccctacaggctgtgataagtgcgtc 1
                     ||||||||||  ||||||||||||||  ||||||  ||||||||||||||||||||||||
Sbjct:          1075 gtaaccggagagtgcttggaagaaggatttgaagtccctacaggctgtgataagtgcgtc 1
laminin, alpha 4 251   V  T  G  E  C  L  E  E  G  F  E  V  P  T  G  C  D  K  C  V

Query:          1094 tgggacctgactgatgacctgcggttagcagcgctctccatcgaggaaggcaaatccggg 1
                     ||||||  ||||  ||||||||||  ||||||||||||||||||||  ||  ||||||||||
```

```
Sbjct:           1135 tgggacttgaccgatgacctgcgattagcagcgctctccatcgaagagagcaaatccggg 1
laminin, alpha 4 271   W  D  L  T  D  D  L  R  L  A  A  L  S  I  E  E  S  K  S  G

Query:           1154 gtgctgagcgtatcctctggggccgccgctcataggcacgtgaatgaaatcaacgccacc 1
                      |||||||||| |||||||| || || || ||||| |||||||  || || ||| | |||
Sbjct:           1195 ctgctgagcgtgtcctctggcgctgcggcgcatagacacgtgaccgacatgaactctacc 1
laminin, alpha 4 291   L  L  S  V  S  S  G  A  A  A  H  R  H  V  T  D  M  N  S  T

Query:           1214 atctacctcctcaaaacaaaattgtcagaaagagaaaaccaatacgccctaagaaagata 1
                      ||| ||||||||| |||||  ||||||||||||||||||| ||  ||||||||||||||
Sbjct:           1255 atccacctcctcagaacaaggctgtcagaaagagaaaaccagtataccctaagaaagata 1
laminin, alpha 4 311   I  H  L  L  R  T  R  L  S  E  R  E  N  Q  Y  T  L  R  K  I

Query:           1274 caaatcaacaatgctgagaacacgatgaaaagccttctgtctgacgtagaggaattagtt 1
                      || || |||||  | ||||||||  ||| |||||| ||| |||| ||||||| | |   |
Sbjct:           1315 cagataaacaactcggagaacacactgagaagcctcctgcctgatgtagagggactccat 1
laminin, alpha 4 331   Q  I  N  N  S  E  N  T  L  R  S  L  L  P  D  V  E  G  L  H

Query:           1334 gaaaaggaaaatcaagcctccagaaaaggacaacttgttcagaaggaaagcatggacacc 1
                      || |||| || ||||||||| ||||| ||    || ||| ||||||||||||||| ||
Sbjct:           1375 gagaagggaagtcaagcctcaagaaagggtatgctggttgagaaggaaagcatggataca 1
laminin, alpha 4 351   E  K  G  S  Q  A  S  R  K  G  M  L  V  E  K  E  S  M  D  T

Query:           1394 attaaccacgcaagtcagctggtagagcaagcccatgatatgagggataaaatccaagag 1
                      ||| |||| |||| || || || |||||||||||  | |||||||| ||||||||||||
Sbjct:           1435 attgaccaagcaacccatcttgtcgagcaagcccacaacatgagggacaaaatccaagag 1
laminin, alpha 4 371   I  D  Q  A  T  H  L  V  E  Q  A  H  N  M  R  D  K  I  Q  E

Query:           1454 atcaacaacaagatgctctattatggggaagagcatgaacttagccccaaggaaatctct 1
                      ||||||| |||||||||||| ||||| ||  | || |||||| ||||| |||||||  ||
Sbjct:           1495 atcaacagcaagatgctctactatggagagaatcaggaacttggccccgaggaaatagct 1
laminin, alpha 4 391   I  N  S  K  M  L  Y  Y  G  E  N  Q  E  L  G  P  E  E  I  A

Query:           1514 gagaagctggtgttggcccagaagatgcttgaagagattagaagccgtcaaccatttttc 1
                      |||||||||||||||||||||||| ||||| |||||||| ||||||| || |||||  ||
Sbjct:           1555 gagaagctggtgttggcccagaaaatgctggaagagatccgaagccggcagccattcctc 1
laminin, alpha 4 411   E  K  L  V  L  A  Q  K  M  L  E  E  I  R  S  R  Q  P  F  L

Query:           1574 acccaacgggagctcgtggatgaggaggcagatgaggcttacgaactactgagccaggct 1
                      ||||| |||||||| |||||||||||||||||||||||  | ||| | |||||||| |||
Sbjct:           1615 acccatcgggagctggtggatgaggaggcagatgaggcccaggaattgctgagccaagct 1
laminin, alpha 4 431   T  H  R  E  L  V  D  E  E  A  D  E  A  Q  E  L  L  S  Q  A

Query:           1634 gagagctggcagcggctgcacaatgagacccgcactctgtttcctgtcgtcctggagcag 1
                      |||| |||||||||||||||||||| |||||| || | || || || || |||||||||
Sbjct:           1675 gagaactggcagcggctgcacaatgacacccgctctttattccccgtggtgctggagcag 1
laminin, alpha 4 451   E  N  W  Q  R  L  H  N  D  T  R  S  L  F  P  V  V  L  E  Q

Query:           1694 ctggatgactacaatgctaagttgtcagatctccaggaagcacttgaccaggcccttaac 1
                      ||||| |||||||| |||||| |||| || ||||||||| |  || ||||||||||  ||
```

```
Sbjct:           1735 ctggacgactacaacgctaagctgtccgacctccaggaatccattaaccaggccctcgac 1
laminin, alpha 4 471   L  D  D  Y  N  A  K  L  S  D  L  Q  E  S  I  N  Q  A  L  D

Query:           1754 catgtcagggatgccgaagacatgaacagggccacagcagccaggcagcgggaccatgag 1
                      ||||||||||||||| |||||||||||  ||  ||||   |   ||  ||||||||||||||||
Sbjct:           1795 catgtcagggatgcagaagacatgaatagagccatcactttcaagcagcgggaccatgag 1
laminin, alpha 4 491   H  V  R  D  A  E  D  M  N  R  A  I  T  F  K  Q  R  D  H  E

Query:           1814 aaacaacaggaaagagtgagggaacaaatggaagtggtgaacatgtctctgagcacatct 1
                      ||||||||  ||  |||||||  ||||||  ||||||||  |||      ||||||||  |  |||
Sbjct:           1855 aaacaacatgagagagtgaaggaacagatggaagttgtgggtgcctctctgagtatgtct 1
laminin, alpha 4 511   K  Q  H  E  R  V  K  E  Q  M  E  V  V  G  A  S  L  S  M  S

Query:           1874 gcggactctctgacaacacctcgtctaactctttcagaacttgatgatataataaagaat 1
                      ||  ||||||||  ||  |  |||||  ||  ||||||   ||||||||||  ||||||||||||
Sbjct:           1915 gcagactctcttaccatacctcagctcactcttgaggaacttgatgagataataaagaat 1
laminin, alpha 4 531   A  D  S  L  T  I  P  Q  L  T  L  E  E  L  D  E  I  I  K  N

Query:           1934 gcgtcagggatttatgcagaaatagatggagccaaaagtgaactacaagtaaaactatct 1
                      ||  ||  ||  ||||||||||||||||||||||||||||  |||  ||  ||||  |||||||||
Sbjct:           1975 gcatctggaatttatgcagaaatagatggagccaaaaatgagctgcaaggaaaactatcc 2
laminin, alpha 4 551   A  S  G  I  Y  A  E  I  D  G  A  K  N  E  L  Q  G  K  L  S

Query:           1994 aacctaagtaacctcagccatgatttagtccaagaagctattgaccatgcacaggacctt 2
                      |||||  ||||||||||  |||||  ||  ||  ||  |||||||  |||||||||  |  |  |||
Sbjct:           2035 aacctgagtaacctcagtcatgacttggttcaggaagctacggaccatgcatacaatctt 2
laminin, alpha 4 571   N  L  S  N  L  S  H  D  L  V  Q  E  A  T  D  H  A  Y  N  L

Query:           2054 caacaagaagctaatgaattgagcaggaagttgcacagttcagatatgaacgggctggta 2
                      |||||  |||||  ||||  |  |||||  ||  ||||||||||||||  ||||||||||||||
Sbjct:           2095 caacaggaagccgatgagctaagcagaaatttgcacagttcagacatgaacgggctggta 2
laminin, alpha 4 591   Q  Q  E  A  D  E  L  S  R  N  L  H  S  S  D  M  N  G  L  V

Query:           2114 cagaaggctttggatgcatcaaatgtctatgaaaatattgttaattatgttagtgaagcc 2
                      ||||||||||||||||||||||||  ||||||||||||||  |  ||||||||  |||||||||
Sbjct:           2155 cagaaggctttggatgcatcaaacgtctatgaaaatatcgccaattatgtcagtgaagcc 2
laminin, alpha 4 611   Q  K  A  L  D  A  S  N  V  Y  E  N  I  A  N  Y  V  S  E  A

Query:           2174 aatgaaacagcagaatttgctttgaacaccactgaccgaatttatgatgcggtgagtggg 2
                      ||  ||||||||||||  |||||  ||||  |  ||||||  ||||||||||||||  |||||||||
Sbjct:           2215 aacgaaacagcagaacttgctctgaatatcactgatcgaatttatgatgctgtgagtggg 2
laminin, alpha 4 631   N  E  T  A  E  L  A  L  N  I  T  D  R  I  Y  D  A  V  S  G

Query:           2234 attgatactcaaatcatttaccataaagatgaaagtgagaacctcctcaatcaagccaga 2
                      |||||  ||  ||  ||||||||||||||  ||||||||||  |||||  ||||||||||||||||
Sbjct:           2275 attgacacgcagatcatttaccataaggatgaaagtgacaaccttctcaatcaagccaga 2
laminin, alpha 4 651   I  D  T  Q  I  I  Y  H  K  D  E  S  D  N  L  L  N  Q  A  R

Query:           2294 gaactgcaagcaaaggcagagtctagcagtgatgaagcagtggctgacactagcaggcgt 2
                      ||  |||||  ||  ||||||||  |||||||  ||||||||||||||||||||  |||||||||
```

```
Sbjct:          2335 gagctgcaggccaaggcagattctagcaatgatgaagcagtggctgacaccagcaggcgt 2
laminin, alpha 4 671   E  L  Q  A  K  A  D  S  S  N  D  E  A  V  A  D  T  S  R  R

Query:          2354 gtgggtggagccctagcaaggaaaagtgcccttaaaaccagactcagtgatgccgttaag 2
                     ||||||||||||||    |||||  | |||||  | |  ||||||  | ||||||  ||||||
Sbjct:          2395 gtgggtggagccctgtggaggaagggcgccctcagagacagactgaatgatgctgttaag 2
laminin, alpha 4 691   V  G  G  A  L  W  R  K  G  A  L  R  D  R  L  N  D  A  V  K

Query:          2414 caactacaagcagcagagagaggggatgcccagcagcgcctggggcagtctagactgatc 2
                     ||||||||  ||||||||||||||||||  |||||  ||||||||||  |||||  |  ||  ||
Sbjct:          2455 caactacaggcagcagagagaggggacgcccaccagcgcctgggccagtccaagctcttc 2
laminin, alpha 4 711   Q  L  Q  A  A  E  R  G  D  A  H  Q  R  L  G  Q  S  K  L  F

Query:          2474 accgaggaagccaacaggacgacgatggaggtgcagcaggccactgccccccatggccaac 2
                     |  ||||||||  ||||  ||||||   ||  ||  ||  ||||  ||  |  ||  |||||  |||
Sbjct:          2515 attgaggaagctaacaagacgacagcggctgtccaacaggttaccacaccaatggctaac 2
laminin, alpha 4 731   I  E  E  A  N  K  T  T  A  A  V  Q  Q  V  T  T  P  M  A  N

Query:          2534 aatctaaccaactggtcacagaatcttcaacattttgactcttctgcttacaacactgca 2
                     ||  ||  |  |||||||||  |||||  ||  ||    ||||||||  |||||  ||  |||||||||
Sbjct:          2575 aacctcagcaactggtcccagaacctgcagacctttgactcatctgcatataacactgca 2
laminin, alpha 4 751   N  L  S  N  W  S  Q  N  L  Q  T  F  D  S  S  A  Y  N  T  A

Query:          2594 gtgaactctgctagggatgcagtaagaaatctgaccgaggttgtccctcagctcctggat 2
                     |||  ||||||||  ||||  |||||  |||||  ||  ||||||||||||||  |||||  ||||||
Sbjct:          2635 gtggactctgctcgggacgcagtgagaaacctcaccgaggttgtcccccagcttctggat 2
laminin, alpha 4 771   V  D  S  A  R  D  A  V  R  N  L  T  E  V  V  P  Q  L  L  D

Query:          2654 cagcttcgtacggttgagcagaagcgacctgcaagcaacgtttctgccagcatccagagg 2
                     ||||||||||  ||  ||||||||||  ||||||||||  ||||||||||||||||||||
Sbjct:          2695 cagcttcgtactgtggagcagaagcggcctgcaagcaacatttctgccagcatccagagg 2
laminin, alpha 4 791   Q  L  R  T  V  E  Q  K  R  P  A  S  N  I  S  A  S  I  Q  R

Query:          2714 atccgagagctcattgctcagaccagaagtgttgccagcaagatccaagtctccatgatg 2
                     ||||||||||||||||||||  |||||  |||||  ||  ||||||||||||||||||||||
Sbjct:          2755 atccgagagctcattgctcaaaccaggagtgtcgcaagcaagatccaagtctccatgatg 2
laminin, alpha 4 811   I  R  E  L  I  A  Q  T  R  S  V  A  S  K  I  Q  V  S  M  M

Query:          2774 tttgatggccagtcagctgtggaagtgcactcgagaaccagtatggatgacttaaaggcc 2
                     ||||||||||||||||||||  |||||||||  |  |  |  ||||  ||||||||  |  ||||||
Sbjct:          2815 tttgatggccagtcagctgtcgaagtgcaccccaaagtcagtgtggatgacctgaaggcc 2
laminin, alpha 4 831   F  D  G  Q  S  A  V  E  V  H  P  K  V  S  V  D  D  L  K  A

Query:          2834 ttcacgtctctgagcctgtacatgaaaccccct 2866
                     |||||  ||  |  |||  ||||||||||  ||  |||
Sbjct:          2875 ttcacatccatcagcttgtacatgaagcctcct 2907
laminin, alpha 4 851   F  T  S  I  S  L  Y  M  K  P  P
```

CPU time: 0.08 user secs. 0.00 sys. secs 0.08 total secs.

Lambda K H

```
    1.33     0.621     1.12

Gapped
Lambda      K       H
    1.33     0.621     1.12


Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 908
Number of extensions: 35
Number of successful extensions: 5
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's gapped: 3
Number of HSP's successfully gapped: 3
Number of extra gapped extensions for HSPs above 10.0: 0
Length of query: 6297
Length of database: 14,193,718,533
Length adjustment: 28
Effective length of query: 6269
Effective length of database: 14,193,718,505
Effective search space: 88980421307845
Effective search space used: 88980421307845
Neighboring words threshold: 0
Window for multiple hits: 0
X1: 11 (21.1 bits)
X2: 15 (28.8 bits)
X3: 26 (50.0 bits)
S1: 15 (29.5 bits)
S2: 23 (44.9 bits)
```